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CALCIUM SALTS AND THE ONSET OF LABOR.*

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In a recent communication[1] we have shown that the colostrum of the normal cow, as well as that of a cow ill with parturient paresis, contains a substance or substances capable of bringing about abortion in pregnant guinea-pigs. It was also shown that the substance or substances in the fresh, normal colostrum which excite the pregnant guinea-pig to premature labor withstand heating to boiling for a short time. We reached the conclusion, therefore, that in this respect the exciting substance of the colostrum resembles the hormones, and the further conclusion would seem to be justified from the experimental evidence obtained in our studies that the onset of labor in the pregnant female is brought about by the internal secretions of the mammary gland. For reasons which we hope to discuss more fully in a subsequent communication, it occurred to us that perhaps calcium salts might prove to be an important factor in the onset of labor.

In this connection it is of interest to observe that W. Blair Bell and Paintland Hick,[2] in their admirable studies on calcium metabolism and the periodic variation of the calcium content of the blood during the menstrual period in woman, foresaw a causal connection between the fall of calcium in the systemic blood and its corresponding increase in the menstrual discharge, and the onset of labor in the pregnant female. They proved conclusively that there is an excretion of calcium during the menstrual period which is coincident with the fall of calcium in the blood. They have also shown that calcium salts exert a definite influence upon the uterine contractions, with the slight but definite rise of blood pressure. According to these authors a slow, forcible, and ryhthmical contraction of the uterus is produced by the action of calcium salts similar in all respects to that seen in labor; and while they were

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[1] *Jour. Infec. Dis.*, 1912, 10, p. 244.

[2] *Brit. Med. Jour.*, 1909, 1, p. 517.

unable to show definitely that labor is produced by the action of calcium salts in the blood their work certainly indicates such a possibility, in that they have shown that the uterine secretions are rich in calcium salts. They are therefore inclined to the belief that while possibly other substances of a hormonic nature may act in conjunction with calcium salts, the latter are probably specific in bringing on the rhythmical, expulsive contractions of the menstruating uterus and the uterus in labor. Later Halford,[1] from observations on the remedial effect of calcium salts in pre-eclamptic conditions in woman also arrived at the conclusion that calcium salts may be responsible for the onset of labor in the pregnant female. So far as we have been able to ascertain, however, no one has yet succeeded in proving experimentally that calcium salts can bring on the onset of labor. That calcium salts can cause the premature onset of labor in pregnant guinea-pigs is evident from the following experiments.

In our previous work on the effect of colostrum on pregnant guinea-pigs we had already tested the effect of normal physiological salt solution (.85 per cent NaCl) by way of control. As was to be expected, such a solution was without visible effect. Accordingly, in the tests about to be described, the several solutions of calcium and other salts employed were made approximately isotonic with a normal saline, containing 0.9 per cent NaCl. We have also included one sodium, potassium, and magnesium salt by way of comparison and control. The calcium salts employed were the lactate and glycerophosphate (Merck's preparations). The sodium, potassium and magnesium lactates were prepared by neutralizing the required amounts of N/1 lactic acid with the calculated amounts of the several bases. All of the solutions employed were exactly neutral to litmus. The additional data are given in the following:

EXPERIMENT 1. *Calcium lactate.*—A sterile solution of calcium lactate was prepared containing 3.25 per cent of $Ca(C_3H_5O_3)_2\ 5H_2O$. On analysis this was found by Mr. O. M. Shedd of this laboratory to contain 0.5910 gm. CaO in 100 c.c. This solution was tested on a pregnant guinea-pig with the following result: A healthy female guinea-pig, weighing 640 gms., in the fifth to seventh week of pregnancy, received by intraperitoneal injection 9 c.c. of the above solution of calcium lactate, at 4 P.M., March 29, 1912. The pig suffered no discomfort from the injection and showed no discomfort during the next two hours. On the following morning, viz., at 9 A.M. on

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[1] *Australas, M. Gaz.*, 1909, 28, p. 595.

March 30, 1912, it was found that this pig had given premature birth to three fetuses, weighing together 140 gms., and measuring 9, 9.5, and 9 cm., respectively. The three fetuses were covered with hair and one of them was covered with membranes. The cotyledons were still found attached to the three fetuses. The mother pig had passed 40 c.c. of urine during the night and now weighed 450 gms. She remained well during the next few days and on April 9 was returned to the piggery.

EXPERIMENT 2. *Calcium glycerophosphate.*—A sterile solution of calcium glycerophosphate (Merck) was prepared containing 1.5634 per cent of $C_3H_5(OH)_2 Ca PO_4H_2O$. On analysis this solution was found by Mr. Shedd to contain 0.3840 gm. CaO in 100 c.c. A healthy female guinea-pig, weighing 670 gms., in the fifth to seventh week of pregnancy, received by intraperitoneal injection 9 c.c. of the above solution of calcium glycerophosphate, at 4 P.M., March 29, 1912. For an hour following the injection this pig showed no discomfort. She then urinated and began to show considerable discomfort, apparently in abdomen. During this interval she rolled around on her sides and lay for short intervals more or less flat on her back and was observed to strain down on the pelvic contents. At the end of the second hour after the injection of the calcium glycerophosphate she was more comfortable and quiet and apparently sleeping. She was then left for the night. At 9 A.M., March 30, 1912, it was found that this pig had given premature birth to one fetus, 11.5 cm. long and weighing 90 gms. The fetus was covered with hair and had one cotyledon attached. The mother had passed 40 c.c. of urine and now weighed 540 gms. This pig remained well during the next few days, although she lost in weight. At the time of her return to the piggery on April 9 she weighed 450 gms. The urine of the two pigs that had aborted under the influence of glycerophosphate and lactate of calcium showed a marked increase in the output of calcium in the urine, during the seven days following the abortion. During this interval the calcium in the urine was found by Mr. Shedd to increase gradually from .016 to .126 per cent CaO. Before the injection of the calcium salts their urine contained only .009 per cent CaO.

EXPERIMENT 3. *Sodium lactate.*—A sterile solution of sodium lactate was prepared containing 1.723 gms. $Na(C_3H_5O_3)$, in 100 c.c., by neutralizing 15.4 c.c. N/1 lactic acid with the required amount of pure sodium hydroxide. A healthy female guinea-pig, in the fifth to seventh week of pregnancy, weighing 950 gms., received by intraperitoneal injection 9 c.c. of the above solution of sodium lactate, at noon on April 1, 1912. The pig struggled a little during the injection but 20 minutes later was comfortable and eating cabbage. On the morning of April 2 this pig was found well. No evidence of premature labor and no diarrhea. At 10:45 A.M., April 3, this pig seemed entirely well and was still pregnant; weight 890 gms. At this time this pig received, by intraperitoneal injection, 2 c.c. of normal human colostrum, made up to 9 c.c. with sterile normal salt solution. The pig suffered no discomfort and was eating cabbage in 15 minutes after the injection. April 4, pig seemed well; no evidence of premature labor. During the night of April 4 she gave premature birth to three fetuses, with three cotyledons attached, weighing altogether 194 gms., and measuring 9.5, 10, and 11 cm. in length, respectively. All of the fetuses were covered with hair and one was still covered with membranes. This pig remained well during the next few days and on April 9 was returned to piggery, weighing 590 gms.

EXPERIMENT 4. *Potassium lactate.*—A sterile solution of potassium lactate was prepared containing 1.9727 gms. $K(C_3K_5O_3)$ in 100 c.c., by neutralizing 15.4 c.c. N/1 lactic acid with the required amount of pure potassium hydroxide. A healthy female guinea-pig, weighing 970 gms. and in the fifth to seventh week of pregnancy, received by intraperitoneal injection 9 c.c. of the above solution of potassium lactate, at 12:15 P.M., April 1, 1912. She struggled a little during the injection, but at 12:30 she was quiet and comfortable. She remained normal during the entire afternoon of April 1. On the morning of April 2 she was found to have a marked diarrhea, otherwise normal. No evidence of premature labor. On April 3 the pig was well, the diarrhea having subsided. Stools formed. No evidence of premature labor. On April 4 this pig was well—no evidence of premature labor. On April 5 it was found that this pig had aborted during the night, giving premature birth to three fetuses, weighing altogether 120 gms. These were covered with hair and measured 10.5, 10, and 9.5 cm. in length. This pig remained well during the next few days. On April 9 she weighed 730 gms. and was returned to piggery.

EXPERIMENT 5. *Magnesium lactate.*—A sterile solution of magnesium lactate was prepared containing 2.3017 gms. $Mg(C_3H_5O_3)_2$ in 100 c.c., by neutralizing 21.1 of N/1 lactic acid with pure magnesium oxide. A healthy female guinea-pig, weighing 900 gms., in the fifth to seventh week of pregnancy, received by intraperitoneal injection 9 c.c. of the above solution of magnesium lactate at 12:30 P.M., on April 1, 1912. She showed no discomfort from the injection, but during a short interval after the injection she manifested a desire to lie down and seemed in a somewhat relaxed condition. During the remainder of the afternoon she remained normal. On the morning of April 2 the pig seemed well but had a marked diarrhea. There was no evidence of premature labor. On April 3 the pig had recovered from the diarrhea. There was no evidence of premature labor. On April 4 the pig seemed well—still no evidence of premature labor. On April 5 she seemed well and weighed 780 gms. No interference with pregnancy. On April 8 she weighed 740 gms. and on this date received by intraperitoneal injection 9 c.c. of a mixture of 25 c.c of normal colostrum of the cow and 5 c.c. of distilled water. The liquid injected was previously heated to 38°. The injection caused some discomfort. On April 9 the pig seemed well and had not aborted. On April 10 she seemed well, weighed 680 gms., and had not aborted. On April 12 she seemed well and had not aborted.

It is evident from these results, therefore, that under certain conditions at least, and so far as we have been able to ascertain under normal conditions of pregnancy, calcium salts in the amounts and at the concentrations indicated above are specific in giving rise to premature onset of labor in pregnant guinea-pigs, within a very short interval following their administration intraperitoneally. In the light of Bell and Hick's observations they do this by causing a rhythmical, expulsive contraction of the pregnant uterus. The fact also that potassium lactate, though greatly slower in its action, can accomplish the same thing is also a matter of interest. That sodium lactate, in the amount and at the concentration here employed, does not bring on the onset of premature labor in the pregnant guinea-pig, is what one might naturally be led to expect from the general inertness of small amounts of sodium salts in the animal organism. The fact also that magnesium lactate, in the amount and at the concentration here employed, is powerless to bring on the onset of labor is also what we would be led to anticipate from the work of Meltzer and Auer[1] on the physiological action of magnesium, which, in the form of its soluble salts, greatly inhibits many vital processes and causes complete relaxation, general anaesthesia, and ultimately death. Our guinea-pig gave some evidence of a slightly relaxed condition immediately following the intraperitoneal injection of magnesium lactate; and in this connection it is interesting to note that thus far fresh, normal colostrum from a healthy cow has failed to bring on the onset of labor in the pig that received the magnesium lactate, indicating possibly a protective action on the part of the magnesium against the calcium salts of the colostrum. We hope to continue these investigations.

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[1] *Am. Jour. Physiol.*, 1908, 21, p. 400.